Security Classification

DOCUMENT CONTROL DATA - R & D

Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified

1. ORIGINATING ACTIVITY (Corporate author)
Aerospace Medical Research Laboratory,
Aerospace Division, Air Force Systems Command,
Wright-Patterson Air Force Base, Ohio 45433

2a. REPORT SECURITY CLASSIFICATION
UNCLASSIFIED

2b. GROUP
N/A

3. REPORT TITLE
ACUTE TOXICITY OF OXYGEN DIFLUORIDE

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)

5. AUTHOR(S) (First name, middle initial, last name)
Harvey V. Davis, Ph.D

6. REPORT DATE
December 1970

7a. TOTAL NO. OF PAGES
12

7b. NO. OF REFS
10

8a. CONTRACT OR GRANT NO.
F 33615-70-C- 1046

8b. PROJECT NO. 6302

c.

d.

9a. ORIGINATOR'S REPORT NUMBER(S)
AMRL-TR-70-102
Paper No. 21

9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)

10. DISTRIBUTION STATEMENT
Approved for public release; distribution unlimited

11. SUPPLEMENTARY NOTES
Conference was arranged by the Toxic Hazards Research Unit of SysteMed Corporation

12. SPONSORING MILITARY ACTIVITY
Aerospace Medical Research Laboratory, Aerospace Medical Div., Air Force Systems Command, W-PAFB, Ohio 45433

13. ABSTRACT

This paper was presented at the Proceedings of the 1st Annual Conference on Environmental Toxicology, sponsored by the SysteMed Corporation and held in Fairborn Ohio on 9, 10, and 11 September 1970. Major technical areas discussed included toxicological evaluation of carbon monoxide, methodology, pathology, atmospheric contaninants, and toxicology of propellants and other military chemicals.

Key words:

Toxicology
Propellants

13

DD FORM 1 NOV 65 1473

AMRL-TR-70-102

PAPER NO. 21

ACUTE TOXICITY OF OXYGEN DIFLUORIDE

Harvey V. Davis, Ph. D.

SysteMed Corporation
Wright-Patterson Air Force Base, Ohio

INTRODUCTION

Because of the potential use of oxygen difluoride (OF_2) being used as an oxidizing fuel in the missile industry, it became necessary to define and characterize the hazards associated with the handling of this compound. The gas has been characterized as a strong oxidizing agent, highly toxic, with properties similar to elemental fluorine. It is colorless at atmospheric temperature and pressure, condensing to a pale yellow liquid at -145 C (American Industrial Hygiene Association, 1967). It is stable in dry air and decomposes to any appreciable extent only at elevated temperatures (Allied Chemical Corporation, 1962).

The inhalation toxicity of OF_2 was first reported by LaBelle who demonstrated the highly toxic nature of the compound by using several species of animals (LaBelle et al, 1945). The assessment of OF_2 toxicity in this study was made by exposing four species of animals (monkeys, dogs, rats and mice) to various concentrations of the gas for 15 and 60 minutes.

METHODS

The OF_2 used was a commercial grade purchased from the Allied Chemical Corporation. Assay data indicated 98% purity, most of the impurities being oxygen with trace amounts of carbon dioxide (CO_2) and carbon tetrafluoride (CF_4).

The gas was diluted with dry nitrogen in the Dilution Facility to give a concentration of approximately 1% OF_2. The large cylinders containing the OF_2-nitrogen mixture were pressurized at 1000 pounds and analyzed for the precise OF_2 concentration, after which the diluted gas was delivered to the Toxicology Laboratory. This procedure was developed to minimize the hazards resulting from a possible accidental exposure.

The gas in diluted form was used for the toxicity studies. All exposures were made in the Longley exposure chamber shown in figure 1. The exhaust from the chamber was passed through a water scrubber, with caustic added, to remove OF_2 from the stack effluent. The MSA Billionaire was the analytical instrument used to monitor the concentration of the gas in the exposure chamber.

Figure 1. LONGLEY EXPOSURE CHAMBER

The exposure consisted of four species of animals: Beagle dogs and Rhesus monkeys of both sexes; male Wistar rats, mean weight 250 grams; male ICR mice, mean weight 35 grams. The usual number of animals in each exposure consisted of 4 monkeys, 4 dogs, 10 rats and 15 mice.

RESULTS

The animals were exposed to various concentrations of the gas for 15 and 60 minute time periods. The evaluation of OF_2 toxicity was made by measuring several physiological and biochemical parameters.

1. Symptomatology was observed during exposure and up to 14 days postexposure.
2. Mortality response was recorded for the same time period.
3. Biochemical and hematological tests were made on a selected number of animals.

4. Gross and histopathology examinations were performed on tissues from animals exposed to both lethal and sublethal concentrations of the gas.
5. The phenomenon of tolerance induction in rodents was examined.

Symptomatology

Outward signs of OF_2 toxicity manifested itself in various forms. During the exposure, respiratory distress was the most common symptom seen in rodents, characterized by a rapid, shallow breathing pattern. Gastrointestinal and upper respiratory tract irritation was seen in both monkeys and dogs, although less severe in monkeys.

Survivors of each species exhibited various forms of dyspnea for several days postexposure. One of the most surprising findings was the lack of skin irritation even in animals exposed to lethal concentrations of the gas. A summary of symptoms observed during the exposure is listed below.

TABLE I

SYMPTOMATOLOGY DURING EXPOSURE

Species	Symptoms
Rats and Mice	Tachypnea Muscular Weakness
Dogs and Monkeys	Gagging Lacrimation Salivating Muscular Weakness Dyspnea Vomiting Tetany

Mortality Response

Animal mortality was recorded for both the 15 and 60 minute time periods. Based on the CT (concentration x time) there was a linear response over the time range studied for each of the species. The following CT values were obtained:

Monkeys	at 60 minutes,	26	ppm	(CT	=	1560)
	15 minutes,	108	ppm	(CT	=	1620)
Dogs	at 60 minutes,	26	ppm	(CT	=	1560)
	15 minutes,	90	ppm	(CT	=	1350)
Rats	at 60 minutes,	2.6	ppm	(CT	=	156)
	15 minutes,	12.7	ppm	(CT	=	191)
Mice	at 60 minutes,	1.5	ppm	(CT	=	90)
	15 minutes,	7.5	ppm	(CT	=	113)

The most significant findings were the differences in mortality response between rodents and the large animal species. This response was an order of a magnitude different and is in agreement with published rodent toxicity data (Cianko, 1961; Dost et al, 1968; Lester and Adams, 1965). There was no available information, however, on the susceptibility of monkeys and dogs to OF_2 intoxication. Monkeys and dogs were found to be less sensitive to the toxic effects of the gas. Based on data obtained from accidental human exposures, it appears that man responds to OF_2 in a manner similar to that observed in monkeys and dogs (MacEwen and Vernot, 1969). The mortality response to the inhaled gas is summarized in tables II, III, IV and V.

TABLE II

SIXTY MINUTE MORTALITY RESPONSE
DOGS AND MONKEYS

Species	No. Exposed	Conc. (ppm)	Mortality Ratios
Monkeys	4	16.0	0/4
Monkeys	4	21.0	1/4
Monkeys	4	32.0	3/4
Dogs	4	8.2	0/4
Dogs	4	16.0	2/4
Dogs	4	21.0	1/4
Dogs	4	32.0	4/4

Monkeys LC_{50} 26.0 ppm
Dogs LC_{50} 26.0 ppm

TABLE III

SIXTY MINUTE MORTALITY RESPONSE
RATS AND MICE

Species	No. Exposed	Conc. (ppm)	Mortality Ratios
Rats	10	2.2	0/10
Rats	10	2.7	7/10
Rats	15	3.0	14/15
Rats	10	4.0	10/10
Mice	15	1.0	5/15
Mice	15	2.2	8/15
Mice	15	4.2	15/15

Rats LC_{50} 2.6 ppm
Mice LC_{50} 1.5 ppm

TABLE IV

FIFTEEN MINUTE MORTALITY RESPONSE
DOGS AND MONKEYS

Species	No. Exposed	Conc. (ppm)	Mortality Ratios
Monkeys	4	60	0/4
Monkeys	4	100	2/4
Monkeys	4	120	2/4
Monkeys	4	140	4/4
Dogs	4	60	0/4
Dogs	4	80	1/4
Dogs	4	100	3/4

Monkeys LC_{50} 108 ppm
Dogs LC_{50} 90 ppm

TABLE V

FIFTEEN MINUTE MORTALITY RESPONSE
RATS AND MICE

Species	No. Exposed	Conc. (ppm)	Mortality Ratios
Rats	10	16.5	9/10
Rats	10	15.2	8/10
Rats	10	13.8	9/10
Rats	10	11.9	1/10
Rats	10	11.0	3/10
Rats	10	10.4	1/10
Rats	10	9.5	0/10
Mice	15	16.5	14/15
Mice	15	15.2	12/15
Mice	15	11.9	15/15
Mice	15	11.0	8/15
Mice	15	9.5	12/15
Mice	15	8.5	4/15
Mice	15	7.5	8/15
Mice	15	5.8	1/15
Mice	15	4.5	8/15

Rats LC_{50} 12.7 ppm
Mice LC_{50} 7.5 ppm

Clinical and Biochemical Tests

Clinical and biochemical tests were performed on selected numbers of dogs and monkeys exposed to various concentrations of the gas. Tests were made immediately after exposure and at various intervals up to 14 days postexposure.

The blood constituents, uric acid, urea, and creatinine were not significantly different from those seen in control animals. This auremic condition was taken as an indication that no functional damage had occurred in renal tissue at any of the time periods tested. There were no significant changes in either serum alkaline phosphatase or glutamic oxaloacetic transaminase (SGOT). Blood glucose was normal and there were no changes seen in the extracellular electrolyte composition.

A study was made to determine the effect of the gas on the blood clotting mechanism in dogs. Tests were made immediately after, twenty-four hours and seven days postexposure. There were no demonstrable differences between control and exposed animals as indicated by normal prothrombin times in all animals tested.

Pathology

Macroscopic changes resulting from the exposure to gaseous oxygen difluoride consisted chiefly of pulmonary damage in all species. At lethal concentrations, massive lung edema and hemorrhage with liver, spleen and kidney congestion were common observations. At sublethal concentrations there were slight to moderate degrees of lung congestion and edema.

Tolerance Induction

One of the last approaches undertaken to study the pharmacological properties of OF_2 was to investigate the phenomenon of tolerance induction. Tolerance is defined as the ability to endure or resist the toxic action of a chemical. This phenomenon has been observed in animal exposures to ozone, nitrogen dioxide, and other compounds classified as respiratory irritants (Fairchild, 1967; Matzen, 1957; Stokinger and Scheel, 1962).

Our investigation was limited to the occurrence and duration of tolerance in rodents, and the characterization of the induction concentration of the gas required to produce tolerance. Mortality response was the only criterion used to determine tolerance.

A group of mice was exposed to induction concentrations of 1.0, 0.50 and 0.25 ppm of OF_2 for 60 minutes. The preexposed groups along with a naive group (control group) were reexposed to multilethal concentrations of the gas for sixty minutes. Tolerance was measured at various periods up to 24 days postexposure. There was no significant tolerance produced, as measured by mortality response, in mice exposed to the induction concentrations of 0.50 and 0.25 ppm of the gas. The group exposed to 1.0 ppm (see table VI) developed tolerance within 24 hours, maximized at 8 days and was still effective 24 days after the initial exposure. This observation seems to indicate that tolerance can be produced in mice when the induction concentration is near the lethal effect level.

TABLE VI

INDUCTION OF OF_2 TOLERANCE IN MICE BY PREEXPOSURE TO 1 PPM

Group	Conc. (ppm)	Post Treatment Time	% Mortality
Naive	3.45	24 Hours	100
Preexposed			60
Naive	4.25	8 Days	100
Preexposed			10
Naive	3.50	24 Days	100
Preexposed			50

SUMMARY

The acute effects of OF_2 inhalation were shown mainly to be respiratory in nature. Tachypnea was the most prominent toxic sign observed in rodents. Upper respiratory and gastrointestinal tract irritations were observed in dogs and monkeys.

The mortality response demonstrated a significant difference in the susceptibility of the various species to the toxic effects of the gas. Rats and mice were found to be much more susceptible than monkeys or dogs. A summary of the mortality response is listed in table VII.

TABLE VII

SUMMARY OF OF_2 DOSE RESPONSE AND LC_{50} VALUES OF ANIMALS

	LC_{50} Values, ppm		CT Dose, ppm-min	
Species	60 Minutes	15 Minutes	60 Minutes	15 Minutes
Monkeys	26	108	1560	1620
Dogs	26	90	1560	1350
Rats	2.6	12.7	156	191
Mice	1.5	7.5	90	113

The most characteristic macroscopic changes were lung edema and hemorrhage. At lethal concentrations, congestion of liver, spleen, and kidney were observed.

REFERENCES

1. American Industrial Hygiene Association; "Hygienic Guide Series on Oxygen Difluoride"; Am. Ind. Hyg. Assoc. J., 28:194, 1967.

2. Cianko, G.M.; "Range Find Tests on Oxygen Difluoride"; Rocketdyne Division, North American Aviation, Inc., Canoga Park, California. Report #1, September 1961.

3. Dost, F.N., D.J. Reed, A. Finch and C.H. Wang; "Metabolism and Pharmacology of Inorganic and Fluorine Containing Compounds"; AMRL-TR-67-224, Aerospace Medical Research Laboratory, Wright-Patterson AFB, Ohio, August 1968.

4. Fairchild, E.J.; "Tolerance Mechanisms"; Arch. Environ. Health, 14:111, 1967.

5. LaBelle, C.W., C.W. Metcalf, G.M. Suter and F.A. Smith; "Studies on the Toxicity of Oxygen Fluoride at Levels of Exposure from 10 to 0.1 ppm by Volume"; University of Rochester Report No. M-1981, 1945.

6. Lester, D. and W.R. Adams; "The Inhalational Toxicity of Oxygen Difluoride"; Am. Ind. Hyg. Assoc. J., 26:562, 1965.

7. MacEwen, J.D. and E.H. Vernot; "Toxic Hazards Research Unit: Annual Technical Report"; AMRL-TR-69-84; Aerospace Medical Research Laboratory, Wright-Patterson AFB, Ohio, 1969.

8. Matzen, R.N.; "Development of Tolerance to Ozone in Reference to Pulmonary Edema"; Amer. J. of Physiol., 190:105, 1957.

9. Oxygen Difluoride Product Data Sheet, Allied Chemical Corporation, General Chemical Division, 40 Rector Street, New York, New York, 1962.

10. Stokinger, H.E. and L.D. Scheel; "Ozone Toxicity: Immunochemical and Tolerance-Producing Aspects"; Arch. Environ. Health, 4:327, 1962.

DISCUSSION

DR. SCHEEL (Laboratory of Toxicology and Pathology, USPHS): Harvey, did you run succinic dehydrogenase on kidney tissue?

DR. DAVIS (SysteMed Corporation): No, we did not.

DR. BACK: I have one question. Do you have any idea about the reason for the tolerance? Increased uptake following the first exposure, or what?

DR. DAVIS: No, I think this is what can be considered a general stress phenomenon. Because it appears that, and I think Dr. Scheel can confirm this, there are about four or five mechanisms of tolerance production which have been noted. So we don't know what it is. I think it's just a general stress phenomenon, and don't ask me what stress is.

DR. DOST: If I may engage in a flight of fancy, we have suggested that the mechanism of OF_2 toxicity is based on the movement of OF_2 as an intact molecule into the pulmonary cell where it reacts with intracellular redox components and then results in the metabolic death of the cell with subsequent functional loss of the cell later, because the cell primarily functions as a diffusion barrier and its metabolic activity is not absolutely essential to gas transport. Now I'm wondering whether a low concentration of OF_2 may be engaging in this type of reaction and resulting in increased synthesis of components that are being destroyed at high concentrations.

DR. DAVIS: This is a possibility and John Mountain has engaged in this type of research with ozone as you know.

DR. LEON: We've been playing around with this increased tolerance using animals exposed to oxygen, and George Kidd at Johnsville has been playing around with it for a number of years. Our feeling is (and I think I would be interested to find out if the same might apply with this compound since it's an oxidizing agent) that the thing that happens with these oxidizing agents is that first you get the development of pulmonary edema. If the pulmonary edema is sublethal, our histologic observations and those of George Kidd have been that it's primarily a perivascular pulmonary edema, and it's our feeling that perhaps residual or vestigial lymphatic drainage channels that were open during the fetal and postnatal period of the animal's life are reopened so that the increased tolerance is brought about by an increased capacity to remove the edematous fluid. Kidd, of course, has shown that if he exposes animals to sublethal concentrations

of oxygen at about 500 torr, he can then expose them to one atmosphere of pure oxygen and there is an increased tolerance and the histologic observation of the lungs of these animals show an opening of the perivascular, supposedly lymph, channels.

DR. DOST: One important aspect of this is the time factor. That is, the animals that are lethally intoxicated with OF_2, let's say at a minimum lethal dose, would probably not die until anywhere from 20 to 40 hours after exposure and there would be really no discernible pathology in these animals for many hours after the exposure. Such an animal examined, at 4 or 6 hours, may have a very minor amount of excess water in cells but other than this they're essentially normal in appearance and they can't be saved. This has been our experience and the experience of some of the very early investigators and I understand this is essentially what you have seen too, isn't it, Harvey?

DR. DAVIS: That's correct, yes. Ozone has been used as a model compound in this tolerance work and in nonedemic concentrations there was some tolerance produced as measured by water content. I think this was done down at Dr. Scheel's laboratory so you can get tolerance without producing edema--we've gotten it with ozone.

DR. SCHEEL: In regard to OF_2, I think we should keep in mind that there are two possibilities here for basic toxicity. The oxidizing action of OF_2 can produce acute injury. But the kind of description that you give here of a 24 hour latency in deaths would fit better the fluoride toxicity that can take place if this hydrolyzes in the tissue and this forms a specific block in respiratory enzymes and I think that possibly some work on urine and fluoride excretion in the kidney with succinic dehydrogenase might explain part of the mechanism here.

DR. DOST: The problem with OF_2 is that in a lethal exposure the animal will probably not contact, let alone absorb, more than about 25 micrograms of fluoride ion in the whole exposure and when this is spread out through the animal it is pretty hard to conceive a fluoride inhibition which demands concentrations of anywhere up to maybe 10^{-3} M.

DR. BACK: Also, it's difficult to find out how much fluoride you've got under those circumstances. It is so small that you can't analyze it by classical techniques, and if you use radiotagged compounds you have to do it within an hour or so or you've lost it. I think the half-life is 28 minutes or some such thing as that. So you've got analytical problems when you start working with fluoride at real low concentrations like this.

DR. HODGE: You spoke of the apparent similarity of man to the larger animals in the toxic response. Has there been, is there evidence available of the application of the present TLV in some industrial situation and has there been a record of exposures and recovery or otherwise? Do we have extensive or any body of information?

DR. DAVIS: I don't think it is very extensive but Dr. MacEwen might want to give you his experience with that.

DR. MAC EWEN: There have been a few accidental exposures in the manufacturing process. They have been undocumented concentrations, they have smelled it, the man gets out and he has some pulmonary problems for a week or so. They have been hospitalized, given supportive therapy, and survived. About a year and a half ago, there was a rather severe exposure of a graduate student at a nearby university and Mr. Vernot and I went up there to investigate the accident. The man was trying to characterize the physicochemical constants of this compound. He was preparing to transfer it from a tank to a glass bottle and through it back in the analytical system. He purged his system, or cleaned his system with benzene beforehand, and apparently had saturated the tygon tubing that he was pulling the OF_2 through and the system blew up. When it blew apart, the tank was unsupported and fell on the floor, bent the valve, so he couldn't shut it off. He ran over to the workbench and grabbed a wrench and got down on his knees over the tank and shut if off. The tank, however, was empty by that time. It was a one pound tank of which only about 300 cc had already been used over the year or so that they had been working with it. Making some estimates of the area where he was working, it is probable that the concentration to which he was exposed was at least 1000 parts per million for about two or three minutes before he left the immediate area. It polluted the whole laboratory building, the smell passed throughout the building and everybody else began to get symptoms too. But mostly, I think, they were sympathetic symptoms because by the time they began to get the symptoms they had heard it was toxic. The man was taken immediately to the hospital, or he hurried to the hospital, because he began to hurt and he was in the hospital for about a week and a half. He began to show improvement about the third day, the edema began to resolve. He was not given much therapy except aerosolization with alcohol, and oxygen by mask when he had trouble breathing. He did survive at that concentration and that kind of puzzled us and that's one of the reasons we went to investigate it because of the acute toxicity data on the rodent that we had read before. From Dr. Hodge's groups' work at Rochester back in the forties and the work of Dr. Scheel we couldn't explain how he could survive this kind of concentration. I think you can see from this data that the dog and monkey have an order of magnitude difference in their LC_{50} from the rodents. I think if you extrapolated that line to a two minute period, which really isn't fair because when you get down to short times like that you aren't even sure you're getting complete absorption, or complete pickup of gas in the lung, but if you extrapolated that line down to about two minutes you would find that it's somewhere around 1000 parts per million and that may explain the man's survival. Now OF_2 stinks, it's been referred to as an odorless gas, but I've smelled it and it smells like garlic to me. That's the best way I can define it.

DR. BACK: This is documented for those who want a copy of what he just said, in last year's report on the THRU in 1969 on the Toxic Hazards Research Unit.